REMARKS

Claims 47-55, 57, 59-60, 63-79, 83-84, 86-89 and 91-98 are all the claims pending in the application. Claims 48-55, 57, 59-60, 63, 67, 69-79, 83-84, 86-89 and 92-98 are withdrawn from consideration. Claims 101-114 are new. Claims 47, 48, 51-52, 55, 64, 67, 68, 69, 72, 74-75, 83-84, 87-89, 92-93, 95 and 99 are hereby amended. Applicants submit that support for the amendments and new claims can be found throughout the specification, the original filed claims, and at for example page 3, lines 8-16, page 4, lines 18-25, page 6, lines 5-17, page 10, lines 1-20, page 11, lines 13-17, page 11, line 28 to page 12, line 25 and page 60, line 8 to page 62, line 15. The amendments do not constitute new matter, and thus entry is respectfully requested.

I. Formal Matter

A. Information Disclosure Statement

Applicants thank the Examiner for returning a signed and initialed copy of the PTO Form SB/08 that accompanied the Information Disclosure Statement filed August 12, 2009, indicating consideration of the references therein.

B. Withdrawn Rejections

Applicants thank the Examiner for withdrawing the objections to the specification. Applicants also thank the Examiner for withdrawing the rejection of Claims 64, 66, 68 and 91 under 35 U.S.C. § 112, second paragraph.

C. Election/Restriction

Applicants note that at least dependent Claims 67 and 99 and new claims 101-114 as amended depend ultimately from elected Claim 64. As a result of the foregoing claim amendments, Claims 67, 99 and 101-114 further define the invention claimed in Claim 64, as

defined in elected Group IV, and thus all the claims are directed to the same invention. Therefore, Claims 67, 99 and 101-114 should be examined on the merits in the instant Application, and the Requirement for Restriction withdrawn.

Furthermore, Applicant respectfully requests pursuant to MPEP § 821.04(a), upon allowance of the claims being examined, any claim that depends from or otherwise contains all the limitations of the allowed claims be rejoined and examined.

II. Rejection under 35 U.S.C. § 103

On page 5 of the Office Action, Claims 47, 64-66, 68, and 91 are rejected under 35 U.S.C. § 103(a) as being unpatentable over McCrea (Molecular Pharmacology 1996, Vol. 49, pg. 927-937)("McCrea") in combination with U.S. Patent 6,171,794 to Burchard ("Burchard") for essentially the reasons of record.

In response to Applicant's argument that neither McCrea nor Burchard teach or suggest monitoring GPCR ligand binding or labeling GPCR ligands, the Examiner states that the features upon which Applicants relies (i.e., GPCR ligand binding) are not recited in the claims. Further, in response to Applicant's arguments that there is no motivation to combine McCrea and Burchard, the Examiner states that measuring receptors directly is a reason to substitute the Burchard's nucleotide with McCrea's nucleoside to generate a BODIPY labeled salmeterol. Further, in response to Applicants' argument that the combination of McCrea and Burchard would not result in a compound that retain pharmalogical activity, the Examiner states that features upon which Applicant relies (attaching a fluorophore in such a way as to retain pharmacological activity) is not recited in the claims.

Applicants respectfully traverse. Initially, the independent claims are herewith amended to recite *inter alia*, that Lig is a ligand selected from a non-peptide GPCR ligand agonist and a

non-peptide GPCR ligand antagonist, wherein the Lig comprises pharmacological activity as an agonist or antagonist for GPCR receptor binding and activation or inhibition, and wherein the compound of formula I or I' retains pharmacological activity as a fluorescent GPCR ligand agonist or fluorescent GPCR ligand antagonist or GPCR receptor binding and activation or inhibition. The claims are further amended to define the linker moiety (L). Thus, contrary to the Examiner's response, the recited features of the claims are expressly recited in the claims.

In determining obviousness, there must be some reason other than hindsight for selectively combining the prior art references to render the claimed invention obvious.[2] In addition to the considerations set forth above, *Graham* and subsequent decisions of the U.S. Court of Appeals for the Federal Circuit hold that certain "objective" evidence relating to obviousness also must be considered. Such objective evidence includes unexpected results, commercial success, a long existing problem that went unsolved, failures of others to achieve the invention, and industry recognition of the claimed invention. For such evidence to be given substantial weight, a nexus must be established between the secondary considerations and the claimed invention, rather than extrinsic influences such as unclaimed or prior art features.

Neither McCrea nor Burchard motivates the skilled person to incorporate a linker moiety, as claimed with a non-peptide GPCR ligand agonist or a non-peptide GPCR ligand antagonist, and a fluorophore, such that the compound of formula I or I' retains pharmacological activity as a fluorescent GPCR ligand agonist or fluorescent GPCR ligand antagonist or GPCR receptor binding and activation or inhibition. McCrea teaches salmeterol, which is a ligand for β_1- and

[2] *Akzo N.V. v. United States Int'l Trade Comm.*, 808 F.2d 1471, 1481, 1 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1986), cert. denied, 482 U.S. 909 (1987); *Interconnect Planning Corp. v. Feil,* 774 F.2d 1132, 1143, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985).

β_2-adrenoceptors and further teaches that cells containing stimulated β_1- and β_2-adrenoceptors accumulate cAMP, which is measured by stimulating C6 cell monolayers with salmeterol and measuring the conversion of radiolabeled adenine (8-[^{3}H]Adenine) into [^{3}H]cAMP. Although McCrea teaches binding of a GPCR ligand to the adrenoceptor GPCR receptor, McCrea fails to teach or provide motivation for one of ordinary skill in the art to overcome the particular obstacles of conjugating non-peptide GPCR ligand agonist or a non-peptide GPCR ligand antagonist, with a fluorescent ligand, such that the compound of formula I or I' retains pharmacological activity as a fluorescent GPCR ligand agonist or fluorescent GPCR ligand antagonist or GPCR receptor binding and activation or inhibition.

In fact, McCrea fails to address modifying a non-peptide GPCR ligand. The first crystal structure of a GPCR (beta-adrenergic receptor) was established as recently as 2007. See Cherezov *et al.*, *High Resolution Crystal Structure of an Engineered Human ß2-Adrenergic G Protein-Coupled Receptor*, Science, 318(5854), 1258-1265 (2007)(attached hereto)[3] and Declaration of Hill and Kellam (submitted herewith). As described in the attached Rule 132 Declaration, although is now known that receptors and ligands have a very specific interaction, akin to a lock and key interaction, the receptor having specific binding sites for their corresponding ligand, the sensitivity of the receptors and their binding was not known at the time of McCrea et al or at the time of the present invention. See Declaration of Hill and Kellam. Moreover GPCRs, in particular differ from almost all other receptors, including other membrane receptors, and even GPCR receptors for peptide ligands, in that the ligand binding site is located

[3] In accordance with M.P.E.P. § 609.05(c), the documents cited herein in support of Applicants' remarks are being submitted as evidence directed to an issue raised in the Official Action, and no fee pursuant to 37 C.F.R. 1.97 or 1.98, or citation on a FORM PTO/SB/08A & B is believed to be necessary.

deep within the transmembrane regions of the receptor. See page 3, lines 14-20 of the specification and Declaration of Hill and Kellam. Hence, binding of a non-peptide GPCR ligand is easily upset by attaching anything to the ligand, whereby a former agonist can fail to bind or at best perform as antagonist on binding, when coupled to a fluorophore. See at least page 2, lines 24-30 of the specification. This is in contrast to other receptors, which typically have an exposed binding site, whereby simple coupling of a fluorescent tag to a ligand can produce a ligand having agonist or antagonist properties, the fluorescent moiety causing minimal steric disruption to the binding. See Declaration of Hill and Kellam and Anderson *et al., Fluorescent staining of acetylcholine receptors in vertebrate skeletal muscle*. J. Physiol. 237, 385–400 (1974)(attached hereto).

Burchard fails to cure the deficinies of McCrea. Burchard is directed to distinguishing nucleic acid sequences by their hybridization properties with nucleic acid probes. Burchard teaches coupling BODIPY 630/650 to a polynucleotide as a probe for hybridizing to sequences extracted from cells. The sequence to be probed is not a receptor and indeed has no similarity to a receptor. Rather, the polynucleotides of Burchard simply align if the probe recognizes corresponding nucleotides in the cell extract. The fluorescent moiety is typically located remote from the aligning sequences and cannot easily interfere with the alignment. Accordingly, Burchard does not provide motiviation to one of ordinary skill in the art to couple BODIPY 630/650 to a non-peptide GPCR ligand or any other chemical entity involved in cell interactions.

Furthermore, in the present case, the Office Action has cited documents that show that the components of the claimed ligand or fluorophore was individually known in the art, however, the Office Action has failed to establish a *prima facie* case of obviousness because none of the documents provide sufficient direction or guidance to provide one of ordinary skill in the art with

a reason to combine the components in the manner claimed by the present invention. Contrary to the Office Action's assertions, it appears the Office Action has used "impermissible hindsight" based on Applicants' disclosure to reach the legal conclusion that the claimed invention is obvious, rather than based upon the "facts gleaned from the prior art." (M.P.E.P. §2142). As discussed below, there is nothing in McCrea nor Burchard to provide one of ordinary skill in the art with an explicit reason to combine the components disclosed in McCrea and Burchard in the manner claimed.

As discussed above, Burchard simply couples a reactive group of BODIPY 630/650 to an available reactive group on the polynucleotide. As discussed in the attached Rule 132 Declaration, one of ordinary skill in the art, if so motivated, to the contrary would encounter difficulties by modifying the ligand of McCrea with a fluorophore. Salmeterol, as taught by McCrea, does not have available reactive sites and one of ordinary skill in the art is therefore required to introduce some means to reactively couple salmeterol and BODIPY 630/650. In fact, neither McCrea nor Burchard teach a universal fluorophore or linker that may be used to attach the compounds. Applicants submit that if one of ordinary skill in the art were to identify a well characterized fluorescent GPCR ligand having agonist or antagonist properties, and then attempt to substitute a different ligand or indeed a different fluorophore, the properties would invariably be affected, and a different combination of linker and fluorophore would be required to provide the required properties for a given ligand. See Baker *et al., Influence of fluorophore and linker composition on the pharmacology of fluorescent adenosine A1 receptor ligands,* British Journal of Pharmacology, 159, 772-785 (2010)(attached hereto), and Declaration of Hill and Kellam. As evidenced by Example A3, described in greater detail below, the linker moiety of the present invention, such as C_1-C_{600} hydrocarbyl, makes it possible to both position the fluorophore with

respect to the binding site and to distance the fluorophore from the binding site, such that the fluorescent ligands can maintain its GPCR agonist or antagonist properties.

The specification, at Example A3 teaches that even if it were possible to directly couple salmeterol and BODIPY 630/650, the compound would not result in an agonist GPCR ligand or antagonist GPCR ligand. See Declaration of Hill and Kellam. Rather, the present, invention, as claimed comprises, *inter alia* suitable sites (linker moiety) that may be used to couple the fluorophore Fl to the non-peptide GPCR ligand. The suitable sites retain the agonist and antagonist properties of the compound. Specifically, in Example A3, Applicants carried out a *de novo* synthesis, in order to attach BODIPY 630/650 to salmeterol. See page 60, line 10 to page 62, line 15. In a first approach, a linker is substituted onto the salmeterol side chain through which the fluorophore is subsequently attached. In the second approach, the native alkyl side chain of salmeterol is replaced with a linker and a fluorophore. In the case of the fluorescent derivative salmeterol, it was reported that "retention of binding, fluorescence and activity are uncertain and must therefore be verified and information provided with the fluorescent ligand, to provide a useful compound." Page 60, line 18 to page 61, line 2. Thus, one of ordinary skill in the art would not be motivated to attach a GPCR ligand to a fluorophore due to the reported failures in binding retention and activity. Therefore, one of ordinary skill in the art would not have been motivated to combine the references in the manner suggested by the Examiner without exercising impermissible hindsight.

Moreover, as discussed above, independent Claims 47, 64 and and 68 are amended herewith to recite that the claimed compounds are non-peptide GPCR ligand agonist or antagonists. As discussed in the attached 132 Declaration, peptide probes and peptide ligands, having reactive end groups available for coupling, present very simplified and different

considerations as compared to non-peptide ligands. See Declaration of Hill and Kellam. Accordingly, one of ordinary skill in the art would not have been motivated to substitute a non-peptide ligand in place of salmeterol and attach a fluorophore. To the contrary, the present invention provides methodology for coupling the complex class of non-peptide ligands.

The claims, as amended, also recite a linker moiety comprising, inter alia, C_1-C_{600} hydrocarbyl. The linkers of the claimed invention allow one of ordinary skill in the art to tailor the linker by length and bulk, and still easily incorporating a linking functionality, such as amino, which reliably gives site-directed binding and gives less non-specific binding. See Declaration of Hill and Kellam. The claimed linkers are also easy to handle in terms of solubility and as simple structures, and any extra and intracellular effects can be predicted, in terms of hydrophilicity, hydrophobicity etc. Furtherstill, Applicants submit that the type of linker affects the GPCR agonist and antagonist properties, and affects the pharmacological properties, none of which is taught or suggested by McCrea or Burchard. See Declaration of Hill and Kellam submitted herewith

The applicant resubmits the argument that, the claimed invention is not a mere recitation of salmeterol plus BODIPY, rather, Applicant's claimed invention, as in amended claims, is related to a compound of formula I incorporating a linker linking a non-peptide GPCR ligand agonist or antagonist and fluorescent moiety, wherein compound of formula I or I' retains pharmacological activity as a fluorescent GPCR ligand agonist or fluorescent GPCR ligand antagonist or GPCR receptor binding and activation or inhibition. Such a formula is neither disclosed nor suggested anywhere in the cited prior art. See MPEP § 2143 ("the prior art reference (or references when combined) must teach or suggest all the claim limitations."). See

also *In re Royka*, 490 F.2d 981 (CCPA 1974) (to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art.").

Finally, as disclosed in Figures 1 and 2 and previously argued in Applicants Amendment of August 12, 2009, Applicants have unexpectedly provided useful compounds incorporating a fluorescent moiety, and to particular advantage a red/blue fluorescent moiety, which are particularly useful for readily determining the compounds GPCR ligand agonist and antagonist properties which make it highly compatible with visualizing the location of the total receptor pool in parallel using green fluorescent protein (GFP)-tagged receptors. See Baker et al. (2010), *supra,* and Declaration of Hill and Kellam.

V. Double Patenting

On page 15 of the Office Action, the Examiner provisionally rejects Claims 47, 64-66, 68, and 91 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 21-24 of co-pending Application No. 11/576,035. Since the double patenting rejection is provisional, Applicant defers addressing the merits of the provisional rejection until one of the cited pending Applications issues in accordance with MPEP § 804(I)(B).[4]

Conclusion

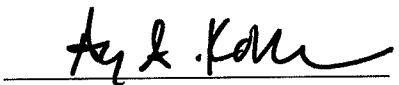
In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the

[4] Deferral of addressing the merits of the rejection is clearly contemplated by MPEP § 804(I)(B), which states that a "provisional" double patenting rejection is designed simply to make Applicants aware of a potential problem. Thus, no response on the merits is required because no patented claims are available to be analyzed.

Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The U.S. Patent and Trademark Office is hereby directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



Azy S. Kokabi
Registration No. 58,902

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

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